Drugs and hepatic transporters: A review

Jetter, Alexander ; Kullak-Ublick, Gerd A

Abstract: The liver is the primary organ for the metabolic degradation of xenobiotics. Transmembrane transport proteins from the ABC and the SLC families mediate the uptake of endogenous compounds and xenobiotics into the hepatocyte as well as their elimination from the cells. Multiple processes are involved. The uptake of xenobiotics in hepatocytes is mediated by organic anion transporting polypeptides (OATPs) and by organic anion and cation transporters (OATs and OCTs). The elimination of drugs and metabolites from the liver cell back to the bloodstream is accomplished mainly by multidrug resistance-associated protein 3 (MRP3) and MRP4, while the elimination towards the biliary canaliculi is mediated by several different transporters (MRP2, BCRP, MDR1 and MATE1). Since bile acids and their salts are toxic detergents for hepatocytes, they have to be eliminated efficiently. This task is accomplished by the bile salt export pump BSEP. Two further transporters, MDR3 and ATP8B1 are involved in the proper constitution of bile. All these transporters can be influenced, mainly inhibited by a number of drugs, but also by metabolites from endogenous compounds such as estrogens. Additionally, rare monogenetic diseases exist which can be explained by absence of function or dysfunction of specific hepatic transporters, such as progressive familial intrahepatic cholestasis type 2 by genetic modifications in BSEP that lead to a loss of transporter function. Functional impairment of other transporters by genetics or by drugs also leads to liver injury, a potentially life-threatening disease that is still not fully understood. Hence, the interplay between drugs and hepatic transporters is multiple, and the knowledge of this interplay helps in understanding the etiology and molecular mechanisms behind some forms of (drug-induced) liver injury.

DOI: https://doi.org/10.1016/j.phrs.2019.04.018

Drugs and hepatic transporters: A review

Alexander Jetter, Gerd A. Kullak-Ublick

Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, Rämistrasse 100, CH-8091 Zürich, Switzerland.

Email for correspondence: alexander.jetter@usz.ch

Abstract

The liver is the primary organ for the metabolic degradation of xenobiotics. Transmembrane transport proteins from the ABC and the SLC families mediate the uptake of endogenous compounds and xenobiotics into the hepatocyte as well as their elimination from the cells. Multiple processes are involved. The uptake of xenobiotics in hepatocytes is mediated by organic anion transporting polypeptides (OATPs) and by organic anion and cation transporters (OATs and OCTs). The elimination of drugs and metabolites from the liver cell back to the bloodstream is accomplished mainly by multidrug resistance-associated protein 3 (MRP3) and MRP4, while the elimination towards the biliary canaliculi is mediated by several different transporters (MRP2, BCRP, MDR1 and MATE1). Since bile acids and their salts are toxic detergents for hepatocytes, they have to be eliminated efficiently. This task is accomplished by the bile salt export pump BSEP. Two further transporters, MDR3 and ATP8B1 are involved in the proper constitution of bile. All these transporters can be influenced, mainly inhibited by a number of drugs, but also by metabolites from endogenous compounds such as estrogens. Additionally, rare monogenetic diseases exist which can be explained by absence of function or dysfunction of specific hepatic transporters, such as progressive familial intrahepatic cholestasis type 2 by genetic modifications in BSEP that lead to a loss of transporter function. Functional impairment of other transporters by genetics or by drugs also leads to liver injury, a potentially life-threatening disease that is still not fully understood. Hence, the interplay between drugs and hepatic transporters is multiple, and the knowledge of this interplay helps in understanding the etiology and molecular mechanisms behind some forms of (drug-induced) liver injury.

Introduction

Besides drug metabolizing enzymes, transmembrane drug transporters exert a relevant influence on the pharmacokinetics, and consequently the pharmacodynamics, of several drugs. These transporters are responsible for either the uptake of drugs into a cell, or for their extrusion from the cell. Mainly two families of transmembrane transporters, which are involved in drug transport, exist: ATP-binding cassette transporters (ABC) and solute carrier transporters (SLC). Transporters from other classes infrequently also play a role in transmembrane drug transport. While SLC-transporters are either uptake or bidirectional transporters, transporters from the ABC family mediate efflux of drugs and metabolites from the cells into the bloodstream or into the bile. Additionally, hepatic transporters may be inhibited by drugs or their metabolites, while they are not transporting these drugs themselves.

Drug transporters in the liver

Since the liver is the main organ responsible for drug metabolism, both the uptake and the efflux of drugs and respective metabolites are in most cases transporter-mediated. The concept of transporter-mediated uptake of compounds into the hepatocytes was first developed when it was shown that the uptake of bile salts at the basolateral side was not a mere passive diffusion, but a carrier-mediated, sodium-dependent process which followed Michaelis-Menten kinetics [1]. Molecular cloning later identified the sodium-taurocholate cotransporting polypeptide NTCP, gene symbol *SLC10A1*, as the responsible transporter [2, 3], which not only transports bile salts across the basolateral membrane of hepatocytes, but also statins [4], and even hepatitis B and D viruses [5, 6].

Basolateral or sinusoidal uptake transporters

Organic anion transporting polypeptides (OATPs)

A number of other transport proteins in the basolateral membrane have been detected, cloned, and functionally characterized since the discovery of transporter-mediated uptake. Namely different members of the family of organic anion transporting polypeptides (OATPs) are present in hepatocytes. Although the first OATP cloned from human liver, OATP1A2 [7], later turned out not to be present in

hepatocytes, but to be mainly expressed in the neurons of the hippocampus and the frontal cortex [8], other members of this family of transporters are strongly expressed in human hepatocytes. The three OATPs most abundantly expressed in the liver are OATP1B1 (gene symbol *SLCO1B1*), OATP1B3 (gene symbol *SLCO1B3*), and OATP2B1 (gene symbol *SLCO2B1*) [9]. These transporters act bidirectionally, and can mediate the uptake of amphipathic and anionic substances in exchange with reduced glutathione or bicarbonate. They have overlapping substrate specificities, which are caused by the high degree of amino acid homology between the three transporters [10]. Numerous endogenous compounds are transported into the hepatocyte by OATPs, but also xenobiotics act as substrates [11]. One of the most important class of drugs which are taken up into the liver cells by OATPs are statins, HMG-CoA-reductase inhibitors [12]. Inhibition of the OATP-mediated uptake of statins into the liver cell leads to increased statin concentrations in the bloodstream and may translate into concentration-dependent adverse effects of statins, such as myopathy. This has been shown e.g. for ciclosporin [13], or gemfibrozil, although the extent of effect may vary according to the pharmacokinetic properties of the statin [14]. Besides statins, methotrexate, fexofenadine, some angiotensin-II-receptor antagonists and angiotensin converting enzyme inhibitors are described as substrates for OATPs [11, 13, 15]. For OATP1B1, it has been shown that the presence of genetic variants which decrease transporter function lead to an increase in drug exposure in the blood (reviewed in [13]). Particularly the c.521T>C SNP (rs4149056) has been shown to increase the AUC of virtually all statins and hence leads to an increased rate of concentration-dependent adverse effects like myopathy. In a genome wide association study on markers for simvastatin toxicity which included more than 300'000 markers in 85 patients with simvastatin-induced myopathy and 90 controls, this SNP in *OATP1B1* was the only functionally active SNP which was strongly associated with statin-induced myopathy [16]. Clinically relevant drug-drug interactions due to inhibition of OATPs may also be expected for several further drugs such as rifampicin [17], octreotide [18] and tyrosine kinase inhibitors, which have been shown in vitro to inhibit hepatic OATP activity. While most tyrosine kinase inhibitors are substrates for OATP1B1 and OATP1B3 [19], pazopanib and nilotinib inhibit OATP1B1 with IC_{50} values of 3.89±1.21 and 2.78±1.13 µM, respectively [20]. It has to be mentioned, however, that tyrosine kinase inhibitors are not selective inhibitors of OATPs, but that also OCT1, OAT3 and other hepatic transporters are inhibited by these drugs, depending on the individual tyrosine kinase inhibitor [21].

There are also inherited diseases linked to OATPs. The human Rotor syndrome, an autosomal recessive disorder characterized by conjugated hyperbilirubinemia, coproporphyrinuria, and practically absent hepatic uptake of anionic diagnostic agents, is caused by genetic variants in *OATP1B1* and *OATP1B3* [22]. Physiologically, bilirubin is conjugated in the hepatocytes mainly by UGT1A1 before a substantial fraction is excreted back into the bloodstream by the multidrug resistance protein 3 (MRP3, *ABCC3*), which is also responsible for the canalicular excretion of bilirubin glucuronides. Thereafter, OATP1B1 and OATP1B3 mediate the reabsorption of conjugated bilirubin into the hepatocytes (so-called “hepatocyte hopping”) [22]. Given the role of human OATP1B1/1B3 as bilirubin (glucuronide) uptake transporters, drug-drug interactions at the basolateral entry site of hepatocytes may lead to a reduced clearance of such endogenous substrates.

Organic anion transporters (OATs)

In addition to the role of OATPs, some members of the organic anion transporters are present in the sinusoidal membrane of hepatocytes. Besides transporting various endogenous compounds such as estrone-3-sulfate, cGMP and others, OAT2 (*SLC22A7*) mediates the uptake of different xenobiotics [23], e.g. entecavir [24] and tolbutamide [25], a clinical marker substrate for CYP2C9 activity [26]. Another OAT, which is present more exclusively in the liver, is OAT7 (*SLC22A9*), while OAT2 is also present in the kidneys. For OAT7, one of the few exogenous substrates, which are known to date, is pravastatin [27].

Organic cation transporters (OCTs)

Like OATs, OCTs are widely distributed throughout tissues and are present mainly in the kidneys, the liver and the intestines [28]. In humans, OCT1 (gene symbol *SLC22A1*) is present mainly in the liver, where it mediates the uptake of positively charged hydrophilic compounds. Metformin is a broadly used antidiabetic which is transported by OCTs, and it has been reported that the OCT1-mediated uptake of metformin can be inhibited by rosiglitazone and repaglinide, two other orally administered antidiabetics [28].

Basolateral efflux transporters

Multidrug resistance-associated proteins (MRP3, MRP4)

These basolateral efflux transporters belong to the class of ABC-transporters. While the aforementioned proteins are located in the basolateral membrane of hepatocytes, MRP2 is located at the canalicular side (see below). Besides expression in the liver, MRPs are present in many other tissues with a barrier function such as the lung, the intestinal cells or the blood-brain-barrier [29]. MRP3 (gene symbol *ABCC3*) and MRP4 (gene symbol *ABCC4*) seem to be present in higher concentrations in the liver. A large range of both endogenous and xenobiotic organic anions is transported by the MRPs. Since they were first discovered in the research elucidating mechanisms of resistance of tumor cells against antineoplastic agents, it is not surprising that among the xenobiotics extruded from the cells by MRPs are vinca alkaloids, methotrexate, alkylating agents, and nucleoside and nucleotide analogs [30]. Glutathione (GSH) plays an important role in the transport mechanism of MRP2, which is not yet fully understood. While some xenobiotics are extruded from the cell as GSH-conjugates, the MRP-mediated transport of others is dependent on, or stimulated by, the presence of GSH at the transporter site [30]. This stimulation of transport of unmodified drugs by GSH has been shown e.g. vinblastine via MRP2 [31] in vitro. In contrast to this, MRP3 does not transport GSH or glutathione-conjugated substances, but shows a preference for glucuronidated compounds [30]. Methotrexate is also transported by MRP3 [29]. In mice, it has been shown that both Mrp3 and Mrp4 are important for the elimination of acetaminophen metabolites from the hepatocytes towards the bloodstream [32, 33], while Mrp2 and Bcrp eliminate acetaminophen conjugates towards the bile [33]. Additionally, in mice, the efflux of morphine glucuronides to the bloodstream was mediated by Mrp3, while Mrp2 was the responsible transport mechanism for biliary elimination of morphine 3-glucuronide, the predominant morphine metabolite [34]. Additionally, MRP3 and MRP4 can also transport bile salts and their glucuronides to the bloodstream, which constitutes a salvage mechanism in the case that the main elimination pathway for bile salts via BSEP is impaired [35]. These findings underline the role of MRPs in the elimination of potentially toxic compounds from the hepatocytes. The expression of MRP4 in the liver seems to be low, as is the case for MRP1 [30]. MRP4 transports a broad range of xenobiotics and contributes to the elimination of bile acids, uric acid, steroid hormones and cyclic nucleotides from the liver cell to the sinusoidal blood [36]. Since its expression is upregulated in cholestasis and other diseases with impaired biliary elimination of organic anions, and since this

upregulation is even more pronounced than the upregulation of MRP3, MRP4 may be an important way of detoxification of bile salts in cholestasis [30].

Canalicular efflux transporters

Bile salt export pump (BSEP)

The bile salt export pump BSEP (gene symbol *ABCB11*) is the primary transporter for the extrusion of bile salts into the bile canaliculi [35], which acts against a steep concentration gradient [37]. Bile salts have detergent properties [38] and may damage mitochondria [39], which leads to cytotoxicity and liver injury [40]. There appears to be no backup transporter for the canalicular export of bile salts, so that the inactivation of BSEP leads to intracellular accumulation of bile salts and hence liver damage. Evidence for this is available both from the bench and from the clinics. An inherited inactivation of BSEP leads to progressive familial intrahepatic cholestasis (PFIC) type 2 [41]. Mutations in *ABCB11* causing less severe reductions in BSEP function have been identified as being causative for benign recurrent intrahepatic cholestasis (BRIC) type 2 [42]. Drugs and / or drug metabolites do not appear to be transported by BSEP, but may act as BSEP-inhibitors. Since the transporter can also be competitively inhibited by ciclosporin, rifampicin, glibenclamide, bosentan and a number of other drugs [35], acquired forms of intrahepatic cholestasis also exist which clinically manifest with elevated transaminases or even as drug-induced liver injury (DILI). However, besides intrahepatic cholestasis caused by transporter inhibition, there are other reasons why DILI may develop, and only some of them are fully understood [43]. A clinically great challenge is the early and specific diagnosis of DILI. Therefore, current research activities focus on the identification and validation of DILI-specific biomarkers [44]. The antidiabetic drug troglitazone was withdrawn from the market because of an elevated incidence of hepatotoxicity. This hepatotoxic potential of troglitazone may be explained by the BSEP-inhibiting properties of the main metabolite troglitazone sulfate [45]. The troglitazone example shows nicely that metabolites which are produced intrahepatically may be the causative agents for inhibition of a transporter function and hence hepatotoxicity. In vitro investigations may hence fail to show hepatotoxic potential of a drug, if only the parent compound and not the metabolites are tested. These findings underline the importance of BSEP for the elimination of bile salts. Bile salts are ligands for the nuclear receptor farnesoid-x-receptor (FXR) and regulate thereby their synthesis, conjugation and transport [46]. FXR ligand-activators may hence be useful in disease states like

cholestatic liver diseases where a FXR-mediated activation of transporter function may be beneficial [47]. Since bile salts play such an important role in some forms of DILI, they could also be useful as biomarkers for DILI caused by BSEP-inhibition [48].

Multidrug resistance-associated protein 2 (MRP2)

The multidrug resistance-associated protein 2 (gene symbol *ABCC2*) is another transporter of the MRP family, which is, in contrast to MRP1, 3, and 4, directed towards the canalicular system. Substrates for this transporter are drug metabolites, including methotrexate [49], acetaminophen-glucuronide [33], ezetimibe and etoposide [50]. MRP2 is also expressed in the kidneys. Particularly in cholestatic conditions, MRP2 is also capable to extrude bile salts from the hepatocytes and thereby helps in mitigating the toxic effect of high intracellular bile salt concentrations [35]. The function of MRP2 is relevant for the biliary elimination of bilirubin-glucuronide. This becomes clear e.g. in patients who have genetic polymorphisms in *ABCC2* which lead, by different mechanisms, to a loss of MRP2 function, and which present with Dubin-Johnson syndrome, a rare, autosomal-recessive, hereditary disease which presents with conjugated hyperbilirubinemia [51]. Estrogen metabolites are involved in the development of cholestasis in women taking oral contraceptives, but also in cholestasis of pregnancy [35]. Estradiol-17β-glucuronide, which is a strongly cholestatic estradiol metabolite in animal experiments [52], has to be excreted into the bile via MRP2 in order to inhibit BSEP from the luminal side and thereby blocking the elimination of bile salts [35].

Breast cancer resistance protein (BCRP)

The expression of BCRP (gene symbol *ABCG2*) is not limited to the liver, as is the case for many other transporters. BCRP shows a broad substrate specificity. As this transporter was first identified in the context of chemotherapy, the irinotecan metabolite SN-38, topotecan, and doxorubicin are examples for BCRP substrates [53]. Also newer drugs like the tyrosine-kinase inhibitor sunitinib are both substrates and inhibitors of BCRP, as it has been shown in humans [54], in rat experiments using pantoprazole as an inhibitor of BCRP [55] and in cells overexpressing BCRP [56]. However, it has to be acknowledged that the impact of hepatic BCRP on the overall pharmacokinetics of BCRP substrates cannot readily be estimated, because BCRP is also present in the intestines and the

kidneys, where the effect of BCRP on the pharmacokinetics of drugs is probably much larger than at the canalicular side of liver cells.

P-glycoprotein (Multidrug resistance gene product 1;MDR1)

P-glycoprotein (gene symbol *ABCB1*) is the most prominent xenobiotic transporter present in virtually all tissues with barrier function. The transporter, which is also called multidrug resistance protein 1 (MDR1), was first discovered and extensively investigated in the context of resistance of tumor cells against antineoplastic agents. The transporter mediates the elimination of a broad variety of xenobiotics from cells, and it shows wide overlap in substrate specificity with other outward-directed drug transporters such as the MRP-transporters MRP3 (at the basolateral hepatocyte membrane) and MRP2 (at the canalicular side of hepatocytes) [57]. Additionally, most drugs transported by MDR1 are also substrates for the most important drug-metabolizing cytochrome P450 enzyme, CYP3A4. The expression of P-glycoprotein at the canalicular membrane of hepatocytes is sevenfold lower than the expression in enterocytes of the small intestines, and a considerable interindividual variation has also been noted [57]. Although more than 100 genetic variants in the ABCB1 gene are known, clinical consequences are at best controversial [58]. The most frequent genetic variants C3435T (rs1045642) or C1236T (rs1128503) do not lead to amino acid exchanges, while the variant G2677T/A (rs2032582) is responsible for an amino acid exchange which appears to cause relatively small changes in P-glycoprotein function [58, 59]. Since MDR1 is expressed in many tissues and cells and appears to be functionally more relevant in the intestines and the blood-brain-barrier in comparison to the hepatocyte, inhibition of MDR1 function by drugs such as verapamil or ritonavir [57, 60] usually leads to pharmacokinetic changes of the victim drug, which cannot be attributed to a single expression site. In summary, it may be possible that MDR1 is not as important in the liver as other drug transporters, and as MDR1 is important in other tissues such as the enterocytes or the endothelial cells at the blood-brain-barrier.

Multidrug resistance gene product 3 (MDR3)

The MDR3 transporter (gene symbol *ABCB4*) is a phosphatidylcholine transporter expressed also at the canalicular membrane of hepatocytes. It translocates phospholipids to the outer leaflet of the

membrane lipid bilayer. Since phospholipids are essential in bile in order to solubilize cholesterol and bile salts in mixed micelles, genetic deficiencies of this transporter lead to a spectrum of cholestatic liver diseases ranging from transient neonatal cholestasis to biliary cirrhosis in adults, some forms of cholelithiasis, but also progressive familial intrahepatic cholestasis type 3, intrahepatic cholestasis of pregnancy, and drug-induced cholestasis [61, 62]. Although the severe loss-of-function variants are rare, up to 60% of a phenotypically healthy European population presents with genetic variants in the *ABCB4* gene [63]. Unlike its close relative MDR1, MDR3 appears to be a phospholipid transporter with no drugs as substrates. However, azole antifungals such as itraconazole, posaconazole and ketoconazole can act as inhibitors of MDR3 and thereby cause cholestatic liver injury, as it has been shown using a functional assay to measure MDR3 activity [64]. When the phospholipid excretion into the bile is inhibited, the bile becomes more toxic because of a reduction in formation of mixed micelles, which mitigate the toxic effect of bile salts towards the biliary epithelium. A number of other compounds has been identified as being inhibitors of MDR3. Most of these compounds are known as causes of drug-induced liver injury and have either been withdrawn from the market or have warnings in the drug information leaflets [65]. Interestingly, azole antifungals like many of these potentially hepatotoxic drugs are also inhibitors of BSEP, thereby leading to a dual mechanism by which they can cause drug-induced liver injury in susceptible patients.

Type 4 P-type ATPase ATP8B1

A third transport mechanism is necessary for appropriate bile formation and avoiding bile salt toxicity: ATP8B1. This canalicular transporter is a phosphatidylserine translocase or flippase. Phosphatidylserines serve to make the outer layer of the membrane more resistant against the detergent properties of bile acids [66]. Rare genetic variants in the ATP8B1 gene lead to a loss of function of this transporter, which manifests clinically as progressive familial intrahepatic cholestasis type 1 (PFIC1), also called Byler's disease, or in less severe cases to benign recurrent intrahepatic cholestasis type 1 (BRIC1) [67, 68].

Multidrug and toxin extrusion protein 1 (MATE1)

MATE transporters are abundantly expressed in the kidneys and play an important role in the tubular elimination of mainly cationic drugs and endogenous compounds [69]. In the canalicular membrane of hepatocytes, MATE1 (gene symbol *SLC47A1*) is expressed, but other MATE proteins have not been found [70]. It has been postulated that MATE1 presents a scavenger transport mechanism to P-glycoprotein, because it shares various neutral and cationic organic substrates with this transporter like fexofenadine, levofloxacin and quinidine, and that substrates which are taken up into the liver cell by OCTs are (at least partially) extruded into the bile by MATE1 [69, 71]. Example substrates for this latter mechanism are metformin and cimetidine. However, MATE1 plays a more important role in the kidneys than in the liver, and data on the specific role of MATE1 in the liver is scarce.

Further hepatic transmembrane transporters

Besides these transmembrane transport proteins which have been relatively well characterized in the liver, other transporters such as the equilibrative nucleoside transporters ENT1 and ENT2 or the organic solute and steroid transporter, OST alpha-OST beta, exist in hepatocytes, but also in intestinal epithelial cells. The latter transporter is an unusual heterodimer, which is important in bile acid and steroid homeostasis. This transport mechanism is mainly expressed in enterocytes, but also on the basolateral membrane of hepatocytes [72]. In hypoxic states, the transport activity of OST alpha-OST beta is induced [73], and it has been shown that this transporter heterodimer can be transactivated by FXR [74], the nuclear receptor that mediates bile acid homeostasis.

Conclusion

The uptake of endogenous and foreign compounds into the liver cell is closely regulated by a number of specific transporters, as is the elimination of such compounds and their metabolites, which are formed intrahepatically towards the bile and back to the bloodstream. A particular function of hepatocytes is the formation of bile, which is both necessary and toxic because of its contents in bile salts. If BSEP, the transporter necessary for proper elimination of bile salts from hepatocytes, is impaired by genetic factors or inhibited by drugs and metabolites, liver injury by intrahepatic cholestasis develops. Functional impairment of other transporters by genetics or by drugs also leads to liver injury, a potentially life-threatening disease, which is still not fully understood. Hence, the

interplay between drugs and hepatic transporters is multiple, and the knowledge of this interplay helps in understanding the etiology and molecular mechanisms behind some forms of (drug-induced) liver injury.

Conflict of interest

None of the authors reports a conflict of interest with regard to this publication.

Acknowledgement

Supported by the Swiss National Science Foundation, SNSF, grant number 310030_175639.

References:

[1] J. Reichen, G. Paumgartner, Uptake of bile acids by perfused rat liver, Am J Physiol 231(3) (1976) 734-42.

[2] B. Hagenbuch, B. Stieger, M. Foguet, H. Lubbert, P.J. Meier, Functional expression cloning and characterization of the hepatocyte Na+/bile acid cotransport system, Proc Natl Acad Sci U S A 88(23) (1991) 10629-33.

[3] B. Hagenbuch, P.J. Meier, Molecular cloning, chromosomal localization, and functional characterization of a human liver Na+/bile acid cotransporter, J Clin Invest 93(3) (1994) 1326-31.

[4] Y.A. Bi, X. Qiu, C.J. Rotter, E. Kimoto, M. Piotrowski, M.V. Varma, A.F. Ei-Kattan, Y. Lai, Quantitative assessment of the contribution of sodium-dependent taurocholate co-transporting polypeptide (NTCP) to the hepatic uptake of rosuvastatin, pitavastatin and fluvastatin, Biopharm Drug Dispos 34(8) (2013) 452-61.

[5] Y. Ni, F.A. Lempp, S. Mehrle, S. Nkongolo, C. Kaufman, M. Falth, J. Stindt, C. Koniger, M. Nassal, R. Kubitz, H. Sultmann, S. Urban, Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes, Gastroenterology 146(4) (2014) 1070-83.

[6] H. Yan, G. Zhong, G. Xu, W. He, Z. Jing, Z. Gao, Y. Huang, Y. Qi, B. Peng, H. Wang, L. Fu, M. Song, P. Chen, W. Gao, B. Ren, Y. Sun, T. Cai, X. Feng, J. Sui, W. Li, Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus, Elife 1 (2012) e00049.

[7] G.A. Kullak-Ublick, B. Hagenbuch, B. Stieger, C.D. Schteingart, A.F. Hofmann, A.W. Wolkoff, P.J. Meier, Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver, Gastroenterology 109(4) (1995) 1274-82.

[8] B. Gao, S.R. Vavricka, P.J. Meier, B. Stieger, Differential cellular expression of organic anion transporting peptides OATP1A2 and OATP2B1 in the human retina and brain: implications for carrier-mediated transport of neuropeptides and neurosteriods in the CNS, Pflugers Arch 467(7) (2015) 1481-1493.

[9] Z.M. Zair, J.J. Eloranta, B. Stieger, G.A. Kullak-Ublick, Pharmacogenetics of OATP (SLC21/SLCO), OAT and OCT (SLC22) and PEPT (SLC15) transporters in the intestine, liver and kidney, Pharmacogenomics 9(5) (2008) 597-624.

[10] G.A. Kullak-Ublick, M.G. Ismair, B. Stieger, L. Landmann, R. Huber, F. Pizzagalli, K. Fattinger, P.J. Meier, B. Hagenbuch, Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver, Gastroenterology 120(2) (2001) 525-33.

[11] A. Kalliokoski, M. Niemi, Impact of OATP transporters on pharmacokinetics, Br J Pharmacol 158(3) (2009) 693-705.

[12] P.J. Neuvonen, M. Niemi, J.T. Backman, Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance, Clin Pharmacol Ther 80(6) (2006) 565-81.

[13] M. Niemi, M.K. Pasanen, P.J. Neuvonen, Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake, Pharmacol Rev 63(1) (2011) 157-81.

[14] Y. Shitara, M. Hirano, H. Sato, Y. Sugiyama, Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2 (OATP2/OATP1B1:SLC21A6)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil, J Pharmacol Exp Ther 311(1) (2004) 228-36.

[15] L. Liu, Y. Cui, A.Y. Chung, Y. Shitara, Y. Sugiyama, D. Keppler, K.S. Pang, Vectorial transport of enalapril by Oatp1a1/Mrp2 and OATP1B1 and OATP1B3/MRP2 in rat and human livers, J Pharmacol Exp Ther 318(1) (2006) 395-402.

[16] Search Collaborative Group, E. Link, S. Parish, J. Armitage, L. Bowman, S. Heath, F. Matsuda, I. Gut, M. Lathrop, R. Collins, SLCO1B1 variants and statin-induced myopathy--a genomewide study, N Engl J Med 359(8) (2008) 789-99.

[17] S.R. Vavricka, J. Van Montfoort, H.R. Ha, P.J. Meier, K. Fattinger, Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver, Hepatology 36(1) (2002) 164-72.

[18] M. Visentin, B. Stieger, M. Merz, G.A. Kullak-Ublick, Octreotide inhibits the bilirubin carriers organic anion transporting polypeptides 1B1 and 1B3 and the multidrug resistance-associated protein 2, J Pharmacol Exp Ther 355(2) (2015) 145-51.

[19] V. Khurana, M. Minocha, D. Pal, A.K. Mitra, Role of OATP-1B1 and/or OATP-1B3 in hepatic disposition of tyrosine kinase inhibitors, Drug Metabol Drug Interact 29(3) (2014) 179-90.

[20] V. Khurana, M. Minocha, D. Pal, A.K. Mitra, Inhibition of OATP-1B1 and OATP-1B3 by tyrosine kinase inhibitors, Drug Metabol Drug Interact 29(4) (2014) 249-59.

[21] R.A. Johnston, T. Rawling, T. Chan, F. Zhou, M. Murray, Selective inhibition of human solute carrier transporters by multikinase inhibitors, Drug Metab Dispos 42(11) (2014) 1851-7.
[22] E. van de Steeg, V. Stranecky, H. Hartmannova, L. Noskova, M. Hrebicek, E. Wagenaar, A. van Esch, D.R. de Waart, R.P. Oude Elferink, K.E. Kenworthy, E. Sticova, M. al-Edreesi, A.S. Knisely, S. Kmoch, M. Jirsa, A.H. Schinkel, Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver, J Clin Invest 122(2) (2012) 519-28.
[23] H. Shen, Y. Lai, A.D. Rodrigues, Organic Anion Transporter 2: An Enigmatic Human Solute Carrier, Drug Metab Dispos 45(2) (2017) 228-236.
[24] T. Furihata, H. Morio, M. Zhu, Y. Suzuki, H. Ide, A. Tsubota, Z. Fu, N. Anzai, K. Chiba, Human organic anion transporter 2 is an entecavir, but not tenofovir, transporter, Drug Metab Pharmacokinet 32(1) (2017) 116-119.
[25] Y.A. Bi, S. Mathialagan, L. Tylaska, M. Fu, J. Keefer, A. Vildhede, C. Costales, A.D. Rodrigues, M.V.S. Varma, Organic Anion Transporter 2 Mediates Hepatic Uptake of Tolbutamide, a CYP2C9 Probe Drug, J Pharmacol Exp Ther 364(3) (2018) 390-398.
[26] A. Jetter, M. Kinzig-Schippers, A. Skott, A. Lazar, D. Tomalik-Scharte, J. Kirchheiner, M. Walchner-Bonjean, U. Hering, V. Jakob, M. Rodamer, W. Jabrane, D. Kasel, J. Brockmoller, U. Fuhr, F. Sorgel, Cytochrome P450 2C9 phenotyping using low-dose tolbutamide, Eur J Clin Pharmacol 60(3) (2004) 165-71.
[27] A. Emami Riedmaier, O. Burk, B.A. van Eijck, E. Schaeffeler, K. Klein, S. Fehr, S. Biskup, S. Muller, S. Winter, U.M. Zanger, M. Schwab, A.T. Nies, Variability in hepatic expression of organic anion transporter 7/SLC22A9, a novel pravastatin uptake transporter: impact of genetic and regulatory factors, Pharmacogenomics J 16(4) (2016) 341-51.
[28] A.T. Nies, H. Koepsell, K. Damme, M. Schwab, Organic cation transporters (OCTs, MATEs), in vitro and in vivo evidence for the importance in drug therapy, Handb Exp Pharmacol (201) (2011) 105-67.
[29] D. Keppler, Multidrug resistance proteins (MRPs, ABCCs): importance for pathophysiology and drug therapy, Handb Exp Pharmacol (201) (2011) 299-323.
[30] R.G. Deeley, C. Westlake, S.P. Cole, Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins, Physiol Rev 86(3) (2006) 849-99.
[31] R. Evers, M. de Haas, R. Sparidans, J. Beijnen, P.R. Wielinga, J. Lankelma, P. Borst, Vinblastine and sulfinpyrazone export by the multidrug resistance protein MRP2 is associated with glutathione export, Br J Cancer 83(3) (2000) 375-83.
[32] M.J. Zamek-Gliszczynski, K. Nezasa, X. Tian, A.S. Bridges, K. Lee, M.G. Belinsky, G.D. Kruh, K.L. Brouwer, Evaluation of the role of multidrug resistance-associated protein (Mrp) 3 and Mrp4 in hepatic basolateral excretion of sulfate and glucuronide metabolites of acetaminophen, 4-methylumbelliferone, and harmol in Abcc3-/- and Abcc4-/- mice, J Pharmacol Exp Ther 319(3) (2006) 1485-91.
[33] M.R. McGill, H. Jaeschke, Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis, Pharm Res 30(9) (2013) 2174-87.
[34] K. van de Wetering, N. Zelcer, A. Kuil, W. Feddema, M. Hillebrand, M.L. Vlaming, A.H. Schinkel, J.H. Beijnen, P. Borst, Multidrug resistance proteins 2 and 3 provide alternative routes for hepatic excretion of morphine-glucuronides, Mol Pharmacol 72(2) (2007) 387-94.
[35] B. Stieger, Role of the bile salt export pump, BSEP, in acquired forms of cholestasis, Drug Metab Rev 42(3) (2010) 437-45.
[36] N. Thakkar, J.R. Slizgi, K.L.R. Brouwer, Effect of Liver Disease on Hepatic Transporter Expression and Function, J Pharm Sci 106(9) (2017) 2282-2294.
[37] B. Stieger, The role of the sodium-taurocholate cotransporting polypeptide (NTCP) and of the bile salt export pump (BSEP) in physiology and pathophysiology of bile formation, Handb Exp Pharmacol (201) (2011) 205-59.
[38] A.F. Hofmann, L.R. Hagey, Key discoveries in bile acid chemistry and biology and their clinical applications: history of the last eight decades, J Lipid Res 55(8) (2014) 1553-95.
[39] S. Krähenbühl, C. Talos, S. Fischer, J. Reichen, Toxicity of bile acids on the electron transport chain of isolated rat liver mitochondria, Hepatology 19(2) (1994) 471-9.
[40] S. Tujios, R.J. Fontana, Mechanisms of drug-induced liver injury: from bedside to bench, Nat Rev Gastroenterol Hepatol 8(4) (2011) 202-11.
[41] E. Jacquemin, Progressive familial intrahepatic cholestasis, Clin Res Hepatol Gastroenterol 36 Suppl 1 (2012) S26-35.
[42] S.W. van Mil, W.L. van der Woerd, G. van der Brugge, E. Sturm, P.L. Jansen, L.N. Bull, I.E. van den Berg, R. Berger, R.H. Houwen, L.W. Klomp, Benign recurrent intrahepatic cholestasis type 2 is caused by mutations in ABCB11, Gastroenterology 127(2) (2004) 379-84.

[43] G.A. Kullak-Ublick, R.J. Andrade, M. Merz, P. End, A. Benesic, A.L. Gerbes, G.P. Aithal, Drug-induced liver injury: recent advances in diagnosis and risk assessment, Gut 66(6) (2017) 1154-1164.
[44] R.J. Church, G.A. Kullak-Ublick, J. Aubrecht, H.L. Bonkovsky, N. Chalasani, R.J. Fontana, J.C. Goepfert, F. Hackman, N.M.P. King, S. Kirby, P. Kirby, J. Marcinak, S. Ormarsdottir, S.J. Schomaker, I. Schuppe-Koistinen, F. Wolenski, N. Arber, M. Merz, J.M. Sauer, R.J. Andrade, F. van Bommel, T. Poynard, P.B. Watkins, Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: An international collaborative effort, Hepatology (2018).
[45] C. Funk, C. Ponelle, G. Scheuermann, M. Pantze, Cholestatic potential of troglitazone as a possible factor contributing to troglitazone-induced hepatotoxicity: in vivo and in vitro interaction at the canalicular bile salt export pump (Bsep) in the rat, Mol Pharmacol 59(3) (2001) 627-35.
[46] J.J. Eloranta, G.A. Kullak-Ublick, The role of FXR in disorders of bile acid homeostasis, Physiology (Bethesda) 23 (2008) 286-95.
[47] Z. Gai, M. Visentin, T. Gui, L. Zhao, W.E. Thasler, S. Hausler, I. Hartling, A. Cremonesi, C. Hiller, G.A. Kullak-Ublick, Effects of Farnesoid X Receptor Activation on Arachidonic Acid Metabolism, NF-kB Signaling, and Hepatic Inflammation, Mol Pharmacol 94(2) (2018) 802-811.
[48] H.S. Schadt, A. Wolf, F. Pognan, S.D. Chibout, M. Merz, G.A. Kullak-Ublick, Bile acids in drug induced liver injury: Key players and surrogate markers, Clin Res Hepatol Gastroenterol 40(3) (2016) 257-266.
[49] M. Masuda, Y. I'Izuka, M. Yamazaki, R. Nishigaki, Y. Kato, K. Ni'inuma, H. Suzuki, Y. Sugiyama, Methotrexate is excreted into the bile by canalicular multispecific organic anion transporter in rats, Cancer Res 57(16) (1997) 3506-10.
[50] C. Fahrmayr, J. Konig, D. Auge, M. Mieth, M.F. Fromm, Identification of drugs and drug metabolites as substrates of multidrug resistance protein 2 (MRP2) using triple-transfected MDCK-OATP1B1-UGT1A1-MRP2 cells, Br J Pharmacol 165(6) (2012) 1836-1847.
[51] A.T. Nies, D. Keppler, The apical conjugate efflux pump ABCC2 (MRP2), Pflugers Arch 453(5) (2007) 643-59.
[52] L. Huang, J.W. Smit, D.K. Meijer, M. Vore, Mrp2 is essential for estradiol-17beta(beta-D-glucuronide)-induced cholestasis in rats, Hepatology 32(1) (2000) 66-72.
[53] Q. Mao, J.D. Unadkat, Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport--an update, AAPS J 17(1) (2015) 65-82.
[54] T. Mizuno, M. Fukudo, T. Terada, T. Kamba, E. Nakamura, O. Ogawa, K. Inui, T. Katsura, Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics, Drug Metab Pharmacokinet 27(6) (2012) 631-9.
[55] S. Kunimatsu, T. Mizuno, M. Fukudo, T. Katsura, Effect of P-glycoprotein and breast cancer resistance protein inhibition on the pharmacokinetics of sunitinib in rats, Drug Metab Dispos 41(8) (2013) 1592-7.
[56] C.L. Dai, Y.J. Liang, Y.S. Wang, A.K. Tiwari, Y.Y. Yan, F. Wang, Z.S. Chen, X.Z. Tong, L.W. Fu, Sensitization of ABCG2-overexpressing cells to conventional chemotherapeutic agent by sunitinib was associated with inhibiting the function of ABCG2, Cancer Lett 279(1) (2009) 74-83.
[57] I. Cascorbi, P-glycoprotein: tissue distribution, substrates, and functional consequences of genetic variations, Handb Exp Pharmacol (201) (2011) 261-83.
[58] S. Wolking, E. Schaeffeler, H. Lerche, M. Schwab, A.T. Nies, Impact of Genetic Polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on Drug Disposition and Potential Clinical Implications: Update of the Literature, Clin Pharmacokinet 54(7) (2015) 709-35.
[59] M. Schaefer, I. Roots, T. Gerloff, In-vitro transport characteristics discriminate wild-type ABCB1 (MDR1) from ALA893SER and ALA893THR polymorphisms, Pharmacogenet Genomics 16(12) (2006) 855-61.
[60] C. Wyen, U. Fuhr, D. Frank, R.E. Aarnoutse, T. Klaassen, A. Lazar, A. Seeringer, O. Doroshyenko, J.C. Kirchheiner, F. Abdulrazik, N. Schmeisser, C. Lehmann, W. Hein, E. Schomig, D.M. Burger, G. Fatkenheuer, A. Jetter, Effect of an antiretroviral regimen containing ritonavir boosted lopinavir on intestinal and hepatic CYP3A, CYP2D6 and P-glycoprotein in HIV-infected patients, Clin Pharmacol Ther 84(1) (2008) 75-82.
[61] C. Lang, Y. Meier, B. Stieger, U. Beuers, T. Lang, R. Kerb, G.A. Kullak-Ublick, P.J. Meier, C. Pauli-Magnus, Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury, Pharmacogenet Genomics 17(1) (2007) 47-60.
[62] E. Gonzales, A. Davit-Spraul, C. Baussan, C. Buffet, M. Maurice, E. Jacquemin, Liver diseases related to MDR3 (ABCB4) gene deficiency, Front Biosci (Landmark Ed) 14 (2009) 4242-56.
[63] C. Pauli-Magnus, R. Kerb, K. Fattinger, T. Lang, B. Anwald, G.A. Kullak-Ublick, U. Beuers, P.J. Meier, BSEP and MDR3 haplotype structure in healthy Caucasians, primary biliary cirrhosis and primary sclerosing cholangitis, Hepatology 39(3) (2004) 779-91.

[64] Z.M. Mahdi, U. Synal-Hermanns, A. Yoker, K.P. Locher, B. Stieger, Role of Multidrug Resistance Protein 3 in Antifungal-Induced Cholestasis, Mol Pharmacol 90(1) (2016) 23-34.
[65] M.D. Aleo, F. Shah, K. He, P.D. Bonin, A.D. Rodrigues, Evaluating the Role of Multidrug Resistance Protein 3 (MDR3) Inhibition in Predicting Drug-Induced Liver Injury Using 125 Pharmaceuticals, Chem Res Toxicol 30(5) (2017) 1219-1229.
[66] D.E. Folmer, R.P. Elferink, C.C. Paulusma, P4 ATPases - lipid flippases and their role in disease, Biochim Biophys Acta 1791(7) (2009) 628-35.
[67] L.N. Bull, R.J. Thompson, Progressive Familial Intrahepatic Cholestasis, Clin Liver Dis 22(4) (2018) 657-669.
[68] G.A. Kullak-Ublick, P.J. Meier, Mechanisms of cholestasis, Clin Liver Dis 4(2) (2000) 357-85.
[69] K. Damme, A.T. Nies, E. Schaeffeler, M. Schwab, Mammalian MATE (SLC47A) transport proteins: impact on efflux of endogenous substrates and xenobiotics, Drug Metab Rev 43(4) (2011) 499-523.
[70] M. Otsuka, T. Matsumoto, R. Morimoto, S. Arioka, H. Omote, Y. Moriyama, A human transporter protein that mediates the final excretion step for toxic organic cations, Proc Natl Acad Sci U S A 102(50) (2005) 17923-8.
[71] K.M. Hillgren, D. Keppler, A.A. Zur, K.M. Giacomini, B. Stieger, C.E. Cass, L. Zhang, C. International Transporter, Emerging transporters of clinical importance: an update from the International Transporter Consortium, Clin Pharmacol Ther 94(1) (2013) 52-63.
[72] N. Ballatori, N. Li, F. Fang, J.L. Boyer, W.V. Christian, C.L. Hammond, OST alpha-OST beta: a key membrane transporter of bile acids and conjugated steroids, Front Biosci (Landmark Ed) 14 (2009) 2829-44.
[73] C.A. Schaffner, J. Mwinyi, Z. Gai, W.E. Thasler, J.J. Eloranta, G.A. Kullak-Ublick, The organic solute transporters alpha and beta are induced by hypoxia in human hepatocytes, Liver Int 35(4) (2015) 1152-61.
[74] J.F. Landrier, J.J. Eloranta, S.R. Vavricka, G.A. Kullak-Ublick, The nuclear receptor for bile acids, FXR, transactivates human organic solute transporter-alpha and -beta genes, Am J Physiol Gastrointest Liver Physiol 290(3) (2006) G476-85.